General

Guideline Title

ACR Appropriateness Criteria® aggressive nonmelanomatous skin cancer of the head and neck.

Bibliographic Source(s)

Koyfman SA, Cooper JS, Beitler JJ, Busse PM, Jones CU, McDonald MW, Quon H, Ridge JA, Saba NF, Salama JK, Siddiqui F, Smith RV, Worden F, Yao M, Yom SS, Expert Panel on Radiation Oncologyâ€“Head & Neck. ACR Appropriateness CriteriaÂ® aggressive nonmelanomatous skin cancer of the head and neck [online publication]. Reston (VA): American College of Radiology (ACR); 2014. 12 p. [38 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

ACR Appropriateness Criteria®

Clinical Condition: Aggressive Nonmelanomatous Skin Cancer of the Head and Neck

Variant 1: 77-year-old woman with mild congestive heart failure and insulin-dependent diabetes presents with a long neglected 8-cm T4N0M0, stage IV nodular BCC of the left temple, involving the forehead and encroaching upon the lateral canthus. CT reveals underlying bony involvement of the facial bones and no evidence of orbital invasion. The wound is oozing and intermittently bleeding, but she is without pain. Her vision remains intact, and she refuses surgical resection. Karnofsky performance score (KPS) 70.

Treatment	Rating	Comments
Conventionally fractionated curative intent RT (e.g., 60–70 Gy in 30–35 fractions)	8	See Table 1 below for commonly used regimens. Assume that some portion of the eye, lachrymal gland, and/or brain needs to be included in the treatment portal.
Palliative intent RT	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. See Table 1 below for commonly used regimens. Assume that some portion of the eye, lachrymal gland, and/or brain needs to be included in the treatment portal.
Rating Scale: 1 2 3 Usually not appropriate; 4 5 6 May be appropriate; 7 8 9 Usually appropriate		

Treatment	Rating	Comments
Hypofractionated curative intent RT (e.g., 40 Gy in 5 fractions)	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. See Table 1 below for commonly used regimens. Assume that some portion of the eye, lachrymal gland, and/or brain needs to be included in the treatment portal.
Best supportive care/hospice	4	
Systemic vismodegib monotherapy	4	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: 57-year-old otherwise healthy woman presents with a neglected 10-cm T4N0M0, stage IV nodular BCC of the posterior and vertex of the scalp, with calvarial involvement on MRI, no frank brain invasion. She undergoes a radical soft-tissue and calvarial resection with titanium mesh closure and anterolateral thigh free-flap reconstruction. She has pathologic evidence of perineural invasion, though margins and dural biopsy are negative. She is healing well at 5 weeks after the operation. KPS 90.

Treatment	Rating	Comments
Adjuvant Recommendations		
Conventionally fractionated curative intent RT	8	See Table 1 below for commonly used regimens.
Hypofractionated curative intent RT	5	See Table 1 below for commonly used regimens. This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. Assume that some portion of the brain needs to be included in the treatment portal.
Observation	3	
Vismodegib	1	
RT + vismodegib	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 3: 46-year-old man presents with an asymptomatic 3-cm moderately differentiated SCC of the right cheek. Contrast-enhanced MRI of the neck reveals the primary lesion without any nodal metastases or cranial nerve abnormalities. He undergoes resection and reconstruction with widely negative margins. No perineural or angiolymphatic invasion is noted. He has healed well postoperatively. KPS 90.

Treatment	Rating	Comments
Adjuvant Recommendations		
Observation	8	
Adjuvant RT to tumor bed alone	2	
Adjuvant RT to tumor bed and V2 nerve pathway	2	
Adjuvant RT to tumor bed, V2 nerve pathway, and ipsilateral facial and cervical lymphatics	2	
Adjuvant systemic therapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 4: 46-year-old man presents with an asymptomatic 3-cm moderately differentiated SCC of the right cheek. Contrast-enhanced MRI of the neck reveals the primary lesion without any nodal or cranial nerve abnormalities. He undergoes resection and reconstruction with widely negative margins. Multifocal perineural invasion is noted pathologically. He has healed well postoperatively. KPS 90.

Treatment	Rating	Comments
Adjuvant Recommendations		
Adjuvant RT to tumor bed and V2 nerve pathway	8	
Adjuvant RT to tumor bed, V2 nerve pathway, and ipsilateral facial and cervical lymphatics	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Observation	3	
Adjuvant RT to tumor bed alone	3	
Adjuvant systemic therapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 5: 58-year-old healthy man with a history of a poorly differentiated 3-cm SCC of the right preauricular region, status post Mohs surgery with negative margin on the second stage of resection with no perineural invasion, presents 6 months later with a right-sided parotid mass. PET/CT reveals a hypermetabolic 3-cm intraparotid mass without any other areas of hypermetabolism. Fine-needle aspiration is positive for SCC.

Treatment	Rating	Comments
Initial Management		
Parotidectomy and neck dissection	8	
Curative intent RT	4	
Curative intent RT with concurrent systemic therapy	4	
Induction chemotherapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 6: Patient described in variant 5 elects for a nerve sparing parotidectomy and an ipsilateral neck dissection. Lymphatic metastases are found in two intraparotid and two level II lymph nodes, with extranodal extension. He is four weeks postop, recovering well. KPS 90.

Treatment	Rating	Comments
Adjuvant Therapy		
RT alone	7	
RT + concurrent cisplatin	7	
RT + concurrent EGFR inhibitor	5	
Systemic therapy alone	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 7: 68-year-old healthy woman with a history of a 2.5-cm moderately differentiated SCC of the right cheek, status post Mohs surgery with negative margins on the third stage of resection and focal perineural involvement, is treated with postoperative radiation to the tumor bed. Nine months later, she presents with pain and numbness in the V2 distribution and diplopia. MRI of brain/neck reveals an enhancing mass in the right base of skull involving the foramen rotundum, Meckel cave, and cavernous sinus, 8 mm from the right optic nerve. The brainstem is uninvolved. No primary site or lymphadenopathy disease is noted. Biopsy is consistent with recurrent SCC. KPS 80.

Treatment	Rating	Comments

Treatment Recommendation Treatment	Rating	Comments
Curative intent RT alone	7	
Curative intent RT + cisplatin	7	
Curative intent RT + EGFR inhibitor	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Systemic therapy alone +/- delayed RT dependent on response	4	
RT Approach		
70 Gy in 35 fractions	8	
74.4 Gy in 62 fractions (1.2 Gy BID)	7	
60 Gy in 30 fractions	5	
40 Gy in 5 fractions using SBRT	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
50 Gy in 20 fractions	4	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 8: 54-year-old man with a history of a liver transplant and a previous 2.5-cm upper lip SCC, status post resection with negative margins 9 months ago presents with biopsy-proven recurrence in his right level IB lymph node. He is currently maintained on FK-506 (tacrolimus) and prednisone 5 mg daily. He undergoes bilateral neck dissections and is found to have 7/54 involved lymph nodes (right level Ib, 2, 4; left level 2) without evidence of extracapsular extension. He recovers well from surgery. KPS 90.

Treatment	Rating	Comments
Adjuvant Recommendations		
RT alone	8	
RT + concurrent cisplatin	5	
RT + concurrent EGFR inhibitor	5	
Systemic therapy alone	1	
RT Targets		
Bilateral cervical nodes levels 1–5 + facial lymphatics	7	
Bilateral cervical nodes levels 1–5	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Bilateral cervical nodes levels 1–5 + facial lymphatics + upper lip primary site	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Immunosuppressive Therapy		
Inform transplant physicians and review possibility for safe reduction of immunosuppression	9	
Continue present immunosuppressive regimen independent of cancer therapy	4	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Summary of Literature Review

Introduction/Background

Although the overwhelming majority of nonmelanomatous and non-Merkel cell skin cancer (NMSC) of the head and neck, specifically basal cell carcinoma (BCC) and squamous cell carcinomas (SCC), is easily cured with surgical removal, superficial radiation therapy (RT), and/or ablation alone, there is a subset of these tumors—either due to neglect or unfavorable biological features—that exhibit aggressive clinical behavior. This subset also includes patients who present with locoregionally advanced disease and experience substantial rates of cancer recurrence and cancer-related morbidity and mortality. The incidence of these cancers is rising, most prominently among the immunosuppressed population. These patients commonly require multimodality therapy and frequently present therapeutic challenges as there is a paucity of high-quality clinical trials to guide clinical decision making. RT plays an important role in the management of these tumors, both in the postoperative and definitive settings.

Characterization of Aggressive Skin Cancer

Aggressive BCC are characterized by a number of high-risk features, including recurrent disease—especially in the setting of prior definitive therapy, infiltrative T4 disease, aggressive pathologic subtypes such as morpheaform, sclerosing, mixed infiltrative, and micronodular histologies, and those rare BCC that demonstrate perineural invasion (PNI). Although BCC arising in the mask areas of the face are also frequently categorized as high-risk, often necessitating advanced surgical or radiation techniques, in the absence of other high-risk features, outcomes are generally quite favorable. Aggressive SCC is more common and is more likely to recur both locoregionally and distantly compared to BCC, and therefore has additional high-risk features that may call for treatment intensification. These include T4 disease, nodal metastases, extensive lymphovascular space or PNI, especially in the setting of neurological symptoms, rapidly growing tumors, satellitosis or in-transit metastases, spindle cell and/or poorly differentiated histology, tumors arising on the ear or non–hair-bearing lip, and deeply invasive tumors (e.g., Clarks level IV/V and/or >2 mm depth).

Recurrence rates vary considerably among cancers that demonstrate one or more of these features, and an additive effect is likely when multiple features are present. As an illustration, although a T2N0 SCC with focal PNI or 4 mm of depth may have a recurrence rate of 5% to 10%, a patient with poorly differentiated T4 disease, those with nodal metastases, and/or those with extensive PNI have a >50% rate of recurrence if treated with single-modality therapy.

Indications for Radiotherapy

Definitive Radiotherapy

Radiotherapy can be used for the definitive treatment of aggressive BCC and SCC. However, surgery is typically preferred for these lesions as it can be done more quickly, and there is some evidence that it may be associated with improved tumor control rates and cosmesis compared to RT alone. A prospective randomized study compared the use of the Mohs surgical technique to definitive RT in 347 patients with BCC of the face <4 cm. Local failure was <1% for patients treated with surgery compared to 7.5% for those treated with RT. Surgical patients also rated their cosmetic outcome as "good" or "better," more commonly (87% versus 69%). Although there was considerable variability in the method and techniques of RT administration (55% via interstitial brachytherapy, 45% with contact or orthovoltage therapy), which compromises the quality of the comparison between groups, this study remains the sole randomized study guiding medical decision making and suggests a benefit for surgery. When performing surgery for these patients, Mohs micrographic surgery is typically favored for lesions of the head and neck based on a prospective randomized study that compared Mohs surgery to wide excision in 612 BCC lesions in a variety of anatomic locations. The 2-year local control (LC) rate was comparable for primary lesions (98%) but superior for recurrent lesions (98% versus 92%). Mohs surgery was also associated with improved cosmesis and lower positive margin rates, especially for BCC with aggressive histologies or in the mask region of the face. Although there are no comparable studies in SCC, this treatment paradigm is often extrapolated to SCC, especially in the head and neck region.

Definitive RT for large or aggressive BCC or SCC is typically reserved for patients who are poor surgical candidates due to advanced age or comorbidities or in patients who strongly prefer nonoperative treatment (see Variant 1 above). In the definitive setting, doses of 60 Gy to 70 Gy in 30 to 35 fractions or accelerated hypofractionated regimens with similar biologically effective tumor dosing is recommended (e.g., 50 Gy to 55 Gy in 20 fractions; 40 Gy to 45 Gy in 10 fractions) to ensure adequate control (see Table 1 below). A large retrospective review of 531 lesions (BCC 389, SCC 142) treated with definitive RT over a 30-year period reported overall control rates of 94% and 89% in the primary setting and 86% and 68% in the recurrent setting for BCC and SCC, respectively. In this report, hypofractionated regimens (>2 Gy/fraction) were associated with improved LC outcomes. This control advantage, however, may come at the price of impaired cosmesis. A large review of >1,000 patients from Germany treated with 4 Gy to 5 Gy/fraction several days weekly to total doses of 50 Gy to 60 Gy reported excellent LC of 95%, but 92% of patients experienced hypopigmentation, and 82% had telangiectasias, recapitulating this concern.

Although radiation monotherapy is often effective for larger tumors, inferior outcomes are seen for T4 tumors, especially those with bony involvement. In the Washington University cohort, for example, patients with T4 tumors had LC rates of 100% and 75% in the primary setting and

67% and 50% in the recurrent setting for BCC and SCC, respectively. Similarly, University of Florida reported their LC with T4 BCC/SCC as 53% at 5 years and an even worse LC in patients who had recurrent disease, bone invasion, or nerve involvement. This observation may support the use of intensified treatment approaches with multimodality therapy in these patients, most often consisting of primary surgery and adjuvant RT, with the goal of improving control rates. This is particularly acute in patients with T3/4 SCC and those with nodal metastases, where rates of locoregional recurrence with definitive RT alone range from 30% to 50%, and cancer-related mortality can be as high as 30%. Although suboptimal, outcomes for advanced primary BCC can be acceptable with definitive RT with 70% to 90% control rates, and should be distinguished from the inferior control rates and higher rates of cancer-related mortality of advanced SCC.

Historically, superficial and orthovoltage techniques have been frequently used in definitive RT for small, and/or superficial skin cancers. Brachytherapy has also been used with excellent control rates for *de novo*, nonaggressive BCC and SCC of the head and neck, especially in cosmetically challenging areas. Aggressive BCC and SCC of the skin, however, can be more infiltrative, and the modest penetration of these modalities into deeper tissues limits their use in these cases. Most often, these lesions will be managed surgically with or without adjuvant RT. However, when primary surgery is not used—either due to unresectable disease or a patient that is medically inoperable or refuses surgery—more deeply penetrating external RT is favored. Electron beam therapy with custom bolus is an excellent choice for patients with targets that are not too thick (typically <4 cm) and encompass a fairly limited field size. For more complex situations that require nodal irradiation, and especially base of skull coverage, more conformal radiation, often using intensity-modulated radiation therapy (IMRT), is preferred to spare surrounding critical structures.

Postoperative Radiotherapy

Postoperative RT is used sparingly for BCC and is reserved for patients with persistently positive margins or large infiltrative T4 tumors that extensively invade bone or soft tissue that would prove difficult to microscopically clear with surgery alone (see Variant 2 above). Even patients with clinically occult, pathologically identified PNI have excellent long-term control rates with surgery alone. For those rare cases that do recur, salvage re-resection with or without adjuvant RT is a viable option with excellent results.

Immunocompetent patients with SCC who have T1–2 tumors that are resected with negative margins without evidence of perineural or lymphovascular space invasion and no evidence of lymph node metastases are well treated with surgery monotherapy (see Variant 3 above). For patients with evidence of any of these high-risk factors, adjuvant RT is typically recommended. Numerous retrospective series have demonstrated that patients with nodal metastases have high rates of recurrence and subsequently benefit from adjuvant RT. A study from Australia revealed improved 5-year disease-free survival (74% versus 34%; P=0.001) and 5-year overall survival (66% versus 27%; P=0.003) for patients treated with postoperative RT compared to surgery alone. Similar to the mucosal head and neck cancer paradigm, an exception pertains to (immunocompetent) patients with a single involved parotid or cervical lymph node on a thorough neck dissection with parotidectomy without evidence of extracapsular spread, who can be treated with surgery monotherapy with low rates (<5%) of recurrence. Patients with large T3 or T4 disease have a significant risk of local recurrence if treated with surgery alone. Occult lymph node metastases are also a concern in such settings, ranging from 29% to 50% for advanced T stage disease, and up to 30% in tumors that are deeply infiltrative (≥8 mm) and/or frankly invade into deep subcutaneous fat.

Another well-reported risk factor for recurrence and a common indication for adjuvant RT in resected cutaneous SCC is PNI. Overall, PNI is found in 5% to 15% of these cancers. The extent of PNI is relevant, as focal PNI has been associated with more favorable outcomes. In a series comprised predominantly of patients treated with resection and adjuvant RT, a group of researchers found that focal PNI was associated with improved relapse-free survival compared to extensive PNI (86% versus 74%; P=0.1). In addition to being associated with a 15% to 25% risk of local recurrence, some studies suggest that the presence of PNI predicts for a higher likelihood of nodal metastases as well, ranging from 5% to 17% in varying studies, and serves as a rationale for elective nodal irradiation in these patients. In the Australian series, patients with recurrent disease that demonstrate PNI at the time of recurrence are at significantly higher risk of recurrence both locally (40% versus 19%; P<0.01) and regionally (29% versus 5%; P=0.02), and strong consideration should be given to elective nodal irradiation in this setting. Site of origin may influence this decision; for example, scalp lesions are less likely to have nodal metastases than nasal or cheek cancers. These data pertain to clinically occult, pathologically determined PNI. Patients with clinically evident PNI, either due to neurological symptoms such as numbness, pain, or facial weakness or radiographic evidence of nerve enhancement, have inferior outcomes with locoregional control rates of only 50% and cancer-related mortality as high as 40%. Importantly, radiographic detection of PNI can be easily overlooked, and careful review with an expert neuroradiologist is crucial in cases where the index of suspicion is high.

When treating patients with PNI, targeting the course of the involved nerves back to the base of skull usually is desirable. Most commonly, branches of the trigeminal and facial nerves are involved. In the former case, when targeting the nerve branches back to their respective foramina in the skull base, including the gasserian ganglion found in Meckel cave and the cavernous sinus (when VI/II are involved) is recommended. For cranial nerve VII involvement, the nerve can be tracked back to the stylomastoid foramen. When targeting this region, care should be taken not to overly restrict dose to the ipsilateral cochlea to ensure adequate coverage of the geniculate ganglion. When nerves are radiographically involved at

the skull base, consideration should be given to targeting the nerve root as it exits the brainstem (see Variant 4 above).

Systemic Therapies

A recent development in metastatic BCC has been the recent approval of the hedgehog pathway inhibitor, vismodegib, based on 30% to 45% response rates in a phase II study of the drug in patients with advanced BCC. It is indicated in patients who have recurrent or metastatic BCC and in patients who are not amenable to definitive resection or RT. This would also include patients with Gorlin syndrome who can develop hundreds of lesions and in whom RT is contraindicated given their inherent radiosensitivity. To date there are no data testing its efficacy in combination with surgery or RT, although clinical trials are underway exploring these potential applications.

In the high-risk cutaneous SCC, there are no randomized studies confirming the added utility of concurrent systemic chemotherapy in conjunction with RT either in the definitive or adjuvant settings. Some clinicians have extrapolated from randomized trials conducted in the mucosal head and neck cancer setting, in which cisplatin-based chemoradiotherapy has demonstrated superior results for locally advanced patients treated nonoperatively, as well as for select high-risk patients requiring postoperative intensification. More recently, there is growing interest in the use of epidermal growth factor receptor (EGFR) inhibitors in this disease either as monotherapy in advanced disease, or in combination with surgery or RT. A recent prospective phase II study investigated the use of the oral tyrosine kinase inhibitor gefitinib as an induction strategy followed by local surgery, RT, or both in patients with locally advanced disease. Of 22 assessable patients, 18% had a complete response, and an additional 27% had a partial response with a promising 2-year progression-free survival of 64%. A different phase I study specifically investigated the addition of the oral tyrosine kinase inhibitor erlotinib concurrently with conventional RT for T4 lesions. The regimen proved safe with a 2-year progression-free survival of 60%. Cetuximab is a monoclonal antibody-based EGFR inhibitor that produced response rates of 30% and disease stabilization rates of 70% when used as monotherapy in a French phase II study of patients with unresectable/metastatic SCC of the skin. Given their substantial activity, these therapies are frequently employed as a concurrent treatment in patients with unresectable, locally advanced cutaneous SCC of the head and neck undergoing definitive RT. However, randomized studies have not yet established a definitive role for these agents in cutaneous SCC of the head and neck, and these approaches remain investigational (see Variant 5, Variant 6 and Variant 7 above).

Considerations in the Immunosuppressed Patient

NMSC is emerging as an increasingly common and dangerous problem for patients who are chronically immunosuppressed. The incidence of BCC and SCC can be 10 fold and 60 to 250 fold higher, respectively, than the general population in patients who have undergone solid organ transplantation, were exposed to extensive chemotherapy, or received longstanding corticosteroid therapy, and affects >20% of all such patients. SCC in particular has a higher likelihood of forming in higher risk sun-exposed areas such as the scalp, lip, and ears.

Immunosuppressed patients more often develop SCC rather than BCC, and they do so at younger ages and with more frequent multifocality, PNI, and deeper infiltration than immunocompetent patients. Once they develop a skin cancer, >75% develop additional lesions within the next 5 years, at times within months of each other. SCC can even account for 5% to 10% of the mortality in these patients. BCC tends to behave fairly similarly independent of immune status. As such, an immunosuppressed patient status is a prominent risk factor for both BCC and SCC, more so for the latter, and often manifests with a more aggressive clinical phenotype. This has significant implications for potentially requiring intensified, multimodality therapy.

Few studies have directly compared outcomes between immunosuppressed and immunocompetent patients with high-risk BCC and SCC. Although adjuvant RT is typically recommended in either case in the presence of high-risk features, it is unclear if disease control rates as well as tolerability of RT differ between these patient cohorts. A group of authors recently reported a retrospective comparison of 38 immunocompetent and 21 immunosuppressed patients treated for cutaneous SCC of the head and neck with resection and adjuvant RT. Most had nodal metastases (63%), 50% had PNI, and 15% were T3/4. Actuarial locoregional control (48% versus 73%; P=0.01) and disease-free survival (44% versus 62%; P=0.03) at 2 years were significantly inferior in the immunosuppressed population. Others have also found immunosuppressed status to portend inferior prognosis in the locally advanced setting. This raises an important unanswered question: Are immunosuppressed patients intrinsically more resistant to traditional adjuvant therapies, or can intensification of therapy with earlier and perhaps dose-escalated RT and/or concurrent systemic therapies improve outcomes? (See Variant 8 above). This question merits future prospective study.

The pattern of spread may also vary in immunosuppressed patients. Discontinuous spread or satellitosis is not uncommon in these patients, and tumors can recur further away from the clinically evident primary tumor site. This may very well be manifestations of field cancerization with separate primary tumors but may have implications for the extent of surrounding tissue that requires targeting in the adjuvant setting, especially in the setting of extensive PNI or lymphovascular space involvement.

Another important consideration in transplant patients relates to their immunosuppression regimens. Calcineurin inhibitors are frequently used to prevent graft rejection in these patients but have been shown to have promitogenic properties. Sirolimus (also known as rapamycin), however, is an mTOR inhibitor with antineoplastic properties and may be preferable in these patients, especially those who have already developed aggressive skin cancers. In a phase III randomized study comparing the use of a calcineurin inhibitor (often FK-506, tacrolimus) with sirolimus in patients with

organ transplants, the latter drug was associated with a significant reduction in the incidence of new SCC (relative risk 0.56; 22% versus 39%; *P*=0.02). Although there were more frequent side effects in the sirolimus group, there was no evidence of higher rates of graft loss. Although a more recently published randomized trial from the Netherlands failed to reproduce these results, it did demonstrate decreased tumor burden with sirolimus-based regimens with moderate increased morbidity. Oral capecitabine, as well as oral retinoids, have also been used with some success as a chemopreventant in these patients (see Variant 8 above). In addition to deciding on the use of adjuvant RT in these high-risk patients, radiation oncologists should consider discussing the risks and benefits of modulation of patients' immunosuppressive regimens with the transplant physicians.

Table 1. Select Examples of Curative RT Regimens
60–70 Gy in 30–35 fractions
50–55 Gy in 17–20 fractions
40–44 Gy in 10 fractions
40 Gy in 5 fractions (twice weekly)
30 Gy in 3 fractions (once weekly)
20–25 Gy in 1 fraction
NOTE: Longer fractionation schedules are preferred when target volumes are in close proximity to neural, optic, and other radiosensitive organs at risk.

Summary of Recommendations

- BCC is highly radiosensitive and is amenable to definitive radiotherapy, especially for those lesions that would entail morbid resection, or in the elderly or infirm.
- In the adjuvant setting, radiotherapy is indicated for recurrent basal cell cancer with persistently positive margins or in large infiltrative tumors that extensively invade bone or soft tissue that would prove difficult to microscopically clear with surgery alone.
- Cutaneous squamous cell cancer that is resected with negative margins and does not display high-risk features can be safely observed postoperatively.
- Resected SCC that demonstrate perineural invasion, especially multifocal, should be considered for adjuvant radiotherapy. A full discussion with the patient of the potential benefits and risks should be documented. In cases of extensive perineural invasion or invasion of named nerves, the nerve should be targeted with radiotherapy back to the skull base.
- Patients with periparotid nodal disease ideally should be managed by surgical resection with neck dissection (and often parotidectomy) followed by adjuvant radiotherapy.
- Concurrent cisplatin-based chemotherapy can be considered, by extrapolation of practices from head and neck mucosal SCC, in patients with high-risk pathologic features (e.g., margin positivity or extracapsular extension) or in the unresectable, locally advanced setting.
- Immunosuppressed patients may experience unusually aggressive clinical tumor behavior and warrant multidisciplinary evaluation.
- Intensified adjuvant therapies, such as radiotherapy for intermediate-risk patients and incorporating systemic therapies concurrently with radiotherapy, may benefit certain classes of patients.
- Management of immunosuppressed patients should include multidisciplinary discussion of long-term plans for immunosuppression and surveillance measures.

Abbreviations

- BCC, basal cell carcinoma
- BID, twice a day
- CT, computed tomography
- EGFR, epidermal growth factor receptor
- KPS, Karnofsky performance score
- MRI, magnetic resonance imaging
- PET/CT, positron emission tomography/computed tomography
- RT, radiation therapy
- SBRT, stereotactic body radiation therapy
- SCC, squamous cell carcinomas

Clinical Algorithm(s)

Algorithms were not developed from criteria guidelines.

Scope

Disease/Condition(s)

Aggressive nonmelanomatous skin cancer of the head and neck

Guideline Category

Management

Risk Assessment

Treatment

Clinical Specialty

Dermatology

Internal Medicine

Oncology

Radiation Oncology

Radiology

Surgery

Intended Users

Health Plans

Hospitals

Managed Care Organizations

Physicians

Utilization Management

Guideline Objective(s)

To evaluate the appropriateness of treatment procedures for patients with aggressive nonmelanomatous skin cancer of the head and neck

Target Population

Patients with aggressive nonmelanomatous skin cancer of the head and neck

Interventions and Practices Considered

1. Radiation therapy (RT)
    - Conventionally fractionated curative intent RT
    - Palliative intent RT
    - Hypofractionated curative intent RT
    - With vismodegib
    - Adjuvant RT (to tumor bed alone; to tumor bed and V2 nerve pathway; to tumor bed, V2 nerve pathway, and ipsilateral facial and cervical lymphatics)
    - Plus concurrent cisplatin
    - Plus concurrent epidermal growth factor receptor (EGFR) inhibitor
    - Curative intent RT with or without concurrent systemic therapy
    - Consideration of approach and targets
2. Best supportive care/hospice
3. Systemic therapy
    - Vismodegib monotherapy
    - Adjuvant systemic therapy
    - Systemic therapy alone +/- delayed RT dependent on response
4. Observation
5. Parotidectomy and neck dissection
6. Induction chemotherapy
7. Immunosuppressive therapy

Major Outcomes Considered

- Local recurrence rate
- Tumor control rates
- Cosmetic outcomes
- Overall and disease-free survival
- Complication rates
- Mortality

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Summary

A literature search was conducted in January 2014 to identify evidence for the *ACR Appropriateness Criteria® Aggressive Nonmelanomatous Skin Cancer of the Head and Neck* topic. Using the search strategy described in the literature search companion (see the "Availability of Companion Documents" field), 444 articles were found. Three articles were used in the topic. Four hundred forty-one articles were not used due to either poor study design, the articles were not relevant or generalizable to the topic, or the results were unclear, misinterpreted, or biased.

The author added 35 citations from bibliographies, Web sites, or books that were not found in the literature search.

See also the American College of Radiology (ACR) Appropriateness Criteria® literature search process document (see the "Availability of Companion Documents" field) for further information.

Number of Source Documents

Three articles were used in the topic. The author added 35 citations from bibliographies, Web sites, or books that were not found in the literature search.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Study Quality Category Definitions

Category 1 - The study is well-designed and accounts for common biases.

Category 2 - The study is moderately well-designed and accounts for most common biases.

Category 3 - There are important study design limitations.

Category 4 - The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:

a. The study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description).
b. The study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence.
c. The study is an expert opinion or consensus document.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The topic author assesses the literature then drafts or revises the narrative summarizing the evidence found in the literature. American College of Radiology (ACR) staff drafts an evidence table based on the analysis of the selected literature. These tables rate the study quality for each article included in the narrative.

The expert panel reviews the narrative, evidence table and the supporting literature for each of the topic-variant combinations and assigns an appropriateness rating for each procedure listed in the variant table(s). Each individual panel member assigns a rating based on his/her interpretation of the available evidence.

More information about the evidence table development process can be found in the ACR Appropriateness Criteria® Evidence Table Development documents (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

Rating Appropriateness

The American College of Radiology (ACR) Appropriateness Criteria (AC) methodology is based on the RAND Appropriateness Method. The appropriateness ratings for each of the procedures or treatments included in the AC topics are determined using a modified Delphi method. A series of surveys are conducted to elicit each panelist's expert interpretation of the evidence, based on the available data, regarding the appropriateness of an imaging or therapeutic procedure for a specific clinical scenario. The expert panel members review the evidence presented and assess the risks or harms of doing the procedure balanced with the benefits of performing the procedure. The direct or indirect costs of a procedure are not considered as a risk or harm when determining appropriateness. When the evidence for a specific topic and variant is uncertain or incomplete, expert opinion may supplement the available evidence or may be the sole source for assessing the appropriateness.

The appropriateness is represented on an ordinal scale that uses integers from 1 to 9 grouped into three categories: 1, 2, or 3 are in the category "usually not appropriate" where the harms of doing the procedure outweigh the benefits; and 7, 8, or 9 are in the category "usually appropriate" where the benefits of doing a procedure outweigh the harms or risks. The middle category, designated "may be appropriate," is represented by 4, 5, or 6 on the scale. The middle category is when the risks and benefits are equivocal or unclear, the dispersion of the individual ratings from the group median rating is too large (i.e., disagreement), the evidence is contradictory or unclear, or there are special circumstances or subpopulations which could influence the risks or benefits that are embedded in the variant.

The ratings assigned by each panel member are presented in a table displaying the frequency distribution of the ratings without identifying which members provided any particular rating. To determine the panel's recommendation, the rating category that contains the median group rating without disagreement is selected. This may be determined after either the first or second rating round. If there is disagreement after the second rating round, the recommendation is "may be appropriate."

This modified Delphi method enables each panelist to articulate his or her individual interpretations of the evidence or expert opinion without excessive influence from fellow panelists in a simple, standardized and economical process. For additional information on the ratings process see the Rating Round Information document on the ACR Web site.

Additional methodology documents, including a more detailed explanation of the complete topic development process and all ACR AC topics can be found on the ACR Web site (see also the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are based on analysis of the current literature and expert panel consensus.

Summary of Evidence

Of the 38 references cited in the *ACR Appropriateness Criteria® Aggressive Nonmelanomatous Skin Cancer of the Head and Neck*

document, all of them are categorized as therapeutic references including six well-designed studies and 12 good quality studies. There are 20 references that may not be useful as primary evidence.

While there are references that report on studies with design limitations, 18 well-designed or good quality studies provide good evidence.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Selection of appropriate procedures for treatment of patients with aggressive nonmelanomatous skin cancer of the head and neck

Potential Harms

- In one study, hypofractionated regimens (>2 Gy/fraction) were associated with improved local control outcomes. This control advantage, however, may come at the price of impaired cosmesis. A large review of >1,000 patients from Germany treated with 4 Gy to 5 Gy/fraction several days weekly to total doses of 50 Gy to 60 Gy reported excellent local control of 95%, but 92% of patients experienced hypopigmentation, and 82% had telangiectasias, recapitulating this concern.
- In a phase III randomized study comparing the use of a calcineurin inhibitor (often FK 506, tacrolimus) with sirolimus in patients with organ transplants, the latter drug was associated with a significant reduction in the incidence of new squamous cell carcinoma (SCC, relative risk 0.56; 22% versus 39%; *P*=0.02). Although there were more frequent side effects in the sirolimus group, there was no evidence of higher rates of graft loss. Although a more recently published randomized trial from the Netherlands failed to reproduce these results, it did demonstrate decreased tumor burden with sirolimus-based regimens with moderate increased morbidity.

Contraindications

Contraindications

Radiation therapy is contraindicated in patients with Gorlin syndrome given their inherent radiosensitivity.

Qualifying Statements

Qualifying Statements

An American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Koyfman SA, Cooper JS, Beitler JJ, Busse PM, Jones CU, McDonald MW, Quon H, Ridge JA, Saba NF, Salama JK, Siddiqui F, Smith RV, Worden F, Yao M, Yom SS, Expert Panel on Radiation Oncologyâ€“Head & Neck. ACR Appropriateness CriteriaÂ® aggressive nonmelanomatous skin cancer of the head and neck [online publication]. Reston (VA): American College of Radiology (ACR); 2014. 12 p. [38 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014

Guideline Developer(s)

American College of Radiology - Medical Specialty Society

Source(s) of Funding

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

Guideline Committee

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology – Head & Neck

Composition of Group That Authored the Guideline

Panel Members: Shlomo A. Koyfman, MD (*Principal Author*); Jay S. Cooper, MD (*Co-author*); Jonathan J. Beitler, MD, MBA; Paul M. Busse, MD, PhD; Christopher U. Jones, MD; Mark W. McDonald, MD; Harry Quon, MD, MS; John A. Ridge, MD, PhD; Nabil F. Saba, MD; Joseph K. Salama, MD; Farzan Siddiqui, MD, PhD; Richard V. Smith, MD; Francis Worden, MD; Min Yao, MD, PhD; Sue S. Yom, MD, PhD (*Panel Chair*)

Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the American College of Radiology (ACR) Web site.

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

Availability of Companion Documents

The following are available:

- ACR Appropriateness Criteria®. Overview. Reston (VA): American College of Radiology; 2015 Feb. 3 p. Electronic copies: Available from the American College of Radiology (ACR) Web site.
- ACR Appropriateness Criteria®. Literature search process. Reston (VA): American College of Radiology; 2015 Feb. 1 p. Electronic copies: Available from the ACR Web site.
- ACR Appropriateness Criteria®. Evidence table development – therapeutic studies. Reston (VA): American College of Radiology; 2013 Nov. 4 p. Electronic copies: Available from the ACR Web site.
- ACR Appropriateness Criteria® aggressive nonmelanomatous skin cancer of the head and neck. Evidence table. Reston (VA): American College of Radiology; 2014. 19 p. Electronic copies: Available from the ACR Web site.
- ACR Appropriateness Criteria® aggressive nonmelanomatous skin cancer of the head and neck. Literature search. Reston (VA): American College of Radiology; 2014. 1 p. Electronic copies: Available from the ACR Web site.

Patient Resources

None available

NGC Status

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